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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,435	08/28/2003	Paul D. Robbins	AP35301 072396.0261	7180

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EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/650,435	ROBBINS ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-16 and 24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. ***Election***

Applicant's election of Group II, claims 17-23, filed 3/22/2006, without traverse is acknowledged.

Claims withdrawn :

Claims 1-16 & 24-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. ***Continuation of prior application***

This application filed under 35 USC 119(e) lacks the necessary reference to the prior application. This application claims the benefit of US Provisional Application No. 06/ , filed ..., should be entered following the title of the invention or as the first sentence of the specification. Also, the present status of all parent applications should be included.

3. ***Priority***

Applicant's claim for domestic priority under 35 U.S.C. 119(e), filed 11 August 2000, is acknowledged.

4. ***Claim Rejections - 35 USC § 112*** (first paragraph)

Written Description

Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to a molecular chaperone and enhancing CFTR channel activity in any cell expressing any mutant CFTR with no defined structure of the

CFTR polypeptide, cell type where expressed or type/specificity of the mutation. [It is not clear what sequences make up the CFTR polypeptides].

The specification does not contain any disclosure or description of the structure(s) and/or function(s) of all CFTR polypeptide sequences having the desired characteristics, the claimed genus. The specification discloses a single CFTR polypeptide species construct that is capable of binding to a cytoplasmic chaperone, such as Hdj2 or Hsc/Hsp70, and enhancing CFTR channel activity in an epithelial cell expressing a mutant CFTR having a deletion of amino acid residue 508, wherein the CFTR polypeptide is linked to a internalizing peptide selected from SEQ ID NO: 1-20, to facilitate the delivery & uptake of the polypeptide into a target cell.

The single disclosed species is not representative of the genus claimed, or is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

5. ***Enablement Rejection***

Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a CFTR polypeptide (specific sequence) species construct that is capable of binding to a cytoplasmic chaperone, such as Hdj2 or Hsc/Hsp70, and enhance CFTR channel activity in an epithelial cell expressing a mutant CFTR having a deletion of amino acid residue 508, wherein the CFTR polypeptide is linked to a internalizing peptide selected from SEQ ID NO: 1-20, does not

reasonably provide enablement for any cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to any molecular chaperone and enhance CFTR channel activity in any cell type expressing any mutant CFTR with no defined structure of the CFTR polypeptide, cell type where expressed or type/specificity of the mutation.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of CFTR polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a single known CFTR polypeptide (250,000 base pairs (250Kb)(*see* specification, page 3) associated with cystic fibrosis as a result of deletion of a phenylalanine residue 508 (ΔF508), and the specific use of internalizing peptide to carry the cargo into the cell, as measured by the presence of functional cargo in the cell.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple deletion or substitution or other modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to any molecular chaperone and enhance CFTR channel activity in any cell type expressing any mutant CFTR with no defined structure of the CFTR polypeptide, cell type where expressed or type/specificity of the mutation.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of exact nature of the CFTR polypeptide having the desired enzymatic characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

6. ***Claim Rejections - 35 USC § 112*** (second paragraph)

Claims 17-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 17, line 1, recites the abbreviation 'CFTR'. The first use of an uncommon abbreviation must be spelt out, which may be abbreviated in the subsequent claims.

(b) Claim 17, line 1, recites 'A CFTR polypeptide comprising amino acid sequences capable...'. The claim is unclear about what sequences comprise the single CFTR polypeptide..'. Clarification is requested.

Claims 18-23 are included in the rejection for failing to correct the defect present in the base claim(s).

7. **35 U.S.C. § 101**

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 17-23 are rejected under 35 U.S.C. § 101 because the claimed invention is directed toward non-statutory subject matter.

In the absence of the hand of man, naturally occurring proteins and/or nucleic acids are considered non-statutory subject matter. *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claim 17 to recite wording such as "An isolated polypeptide".

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17-18 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Meacham et al. [The EMBO Journal, 18(6): 1492-1505 (1999). Meacham et al. describe cystic fibrosis transmembrane conductance regulator (CFTR) polypeptides as a chloride ion channel and therefore has CFTR channel activity, and which comprises two membrane-spanning domains (MSDs), two nucleotide-binding domains (NBD) and a regulatory (R) domain. Human DnaJ 2 (Hdj-2) is a co-chaperone of heat shock cognate 70 (Hsc70) which is localized to the cytosolic face of the ER. They report that immature ER forms of CFTR and ΔF508 CFTR can be isolated in complexes with Hdj-2 and Hsc70, indicating binding. The ΔF508 mutation is localized in NBD1 and causes the CFTR to misfold. Levels of complex formation between ΔF508 CFTR and Hdj-2/Hsp70 were ~2-fold higher than those with CFTR. The earliest stage at which Hdj-2/Hsc70 could bind CFTR translation intermediates coincided with the expression of NBD1 in the cytosol. The reference teaches all the claim limitations and therefore anticipatory. *See* abstract and the entire article.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19-20 & 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meacham et al. [The EMBO Journal, 18(6): 1492-1505 (1999), as applied to claims 17-18 & 21 above, and further in view of USP 6,881,825 (Robbins et al. filing date August 31, 2000).

The teachings of Meacham et al. are described above in paragraph 8. Meacham et al. do not teach the internalizing polypeptides of SEQ ID NO: 1-20 to facilitate uptake and transport of cargo into the cytoplasm.

Robbins et al. teach a number a internalizing polypeptides to facilitate uptake and transport of cargo into the cytoplasm, including the sequences of SEQ ID Nos. 1-3 (claims 22 & 23), which are 100% identical to SEQ ID NO: 4, 5 and 21 respectively of the Robbins patent, as judged by eye-balling the sequences. *See* Tables 1-5, for example. The reference further teaches secretion leader sequences as well ability of the internalizing peptides to efficiently internalize cargo in wide variety of cell types both *in vivo* and *in vitro*. Robbins et al. further show the ability of the internalizing peptides to efficiently internalize cargo in the cell, e.g., the presence of **CFTR** protein may be demonstrated by the presence of functional chloride ion channel

in a cell original lacking CFTR (*see* column 11, lines 66-67 & column 12, lines 1-15).

It would have been obvious to one of ordinary skill in the art to more efficiently express the CFTR polypeptide of Meacham et al. by incorporating the internalizing peptides of Robbins to efficiently carry cargo into the cell, by way of enhanced CFTR channel activity and expression, as such a teaching is not only suggested but is also demonstrated in the works of Robbins et al. One of ordinary skill in the art would have been motivated to combine the teachings of Meacham et al. and Robbins et al. in view of the importance of cystic fibrosis research to humans and more particularly the biogenesis of CFTR polypeptide having enhanced CFTR channel activity.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, *prima facie* obvious.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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